REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of Claims

Claims 1-26, 32, 33-35, 37-40 and 41 were pending. Claims 26-31 were withdrawn in a restriction response dated September 18, 2009. Examiner has withdrawn claims 20, 22, 24, and 26 in the Office Action dated February 19, 2010. With this submission, claims 1-7, 9, 13, 15, 16, 33 and 37 have been amended, claims 8, 10, 11, 12, 14 and 18 have been canceled. No claims have been newly added. Hence, upon entry of this paper, claims 1-7, 9, 13, 15, 16, 17, 19-25-41 will remain pending and under active consideration.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claims remain under examination in the application, is presented, with an appropriate defined status identifier.

II. Restriction Requirement

The Examiner states that "claims 20, 22, 24, and 26 [are] withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim." (Office Action, page 2).

Claim 20, 22, 24, and 26 read on the elected species. For example, SEQ ID NO.: 96 in claim 1 comprises the amino acid sequence YYDDHYCLDY, which is found in SEQ ID NO.: 30 of claim 20 at positions 99-108. Each of the amino acid sequences described in claims 20, 22, 24, and 26 contain the YYDDHYCLDY (SEQ ID NO:96) sequence elected by Applicants in the reply filed on November 20, 2009. Because claims 20, 22, 24 and 26 all depend from claim 1 and contain an elected amino acid sequence, Applicants respectfully traverse the withdrawal of these claims as "being drawn to a nonelected species."

Applicants note that the restriction requirement required election between Group I and Group II. Group I encompassed claims 1-26, 32, 33 in part, 34, 35 37-40 and 41. Claim 20

depends from claim 19, which in turn depends from claim 1, and thus is encompassed in the elected species. Similarly, claim 22 depends from claim 21, which in turn depends from claim 1, and thus is encompassed in the elected species. Claim 24 depends from claim 23 which in turn depends from claim 1, and thus is encompassed in the elected species. Claim 26 depends from claim 23 which in turn depends from claim 1, and thus is encompassed in the elected species.

III. Priority

Applicants attach a petition to accept an unintentionally delayed claim for priority to receive the benefit of the filing date of the international application EP 03 02 3581.6.

IV. Objections to the Specification

A. Abstract of the Disclosure

The abstract of the disclosure is objected to because it contains legal phraseology. Applicants have amended the specification to remove legal phraseology such as "means' and "said" as suggested by the Examiner.

B. SEQ ID NOs

The disclosure is objected to because the Examiner asserts that the specification contains sequences on pages 11 and 85 that are not identified and do not appear to be included in the sequence listing. In this regard:

Applicants contend that the sequences disclosed on page 11, lines 9-25 ("Ile-Tyr," "Val-Tyr," "Ile-Phe," "Phe-Gly-Xaa-Gly," "Lys/Arg-Leu/Ile/Val/Phe/Thr/Ala-Thr/Ser/Ile/Ala," "Cys-Xaa-Xaa," "Cys-Ala-Arg" and "Trp-Gly-Xaa-Gly"), all contain fewer than four specifically defined amino acid residues (specifically defined meaning those amino acids other than "Xaa" – see 37 CFR §1.821(a)), and therefore, do not meet the requirements for inclusion in a Sequence Listing. That said, Applicants respectfully request the removal of the Examiner's request for the inclusion of the above sequences.

In addition, Applicants contend that the sequences disclosed on page 85 have been previously identified as SEQ ID NOS 233, 411, 233 and 233, respectively in order of

appearance, in the amendment of record as filed with the U.S. Patent Office on December 4, 2006, and have also been included in the Sequence Listing as filed. Therefore, Applicants respectfully request the removal of the Examiner's request for the insertion of identifiers for the sequence disclosed on page 85.

C. Browser Executable Code

The disclosure is objected to because it contains an embedded hyperlink. Applicants have amended the specification on pages 11 and 69 to remove the embedded hyperlink as suggested by the Examiner.

Applicants believe that these amendments to the specification traverse all the objections to the specification made by the Office. Therefore, Applicants respectfully request withdrawal of the objections.

V. Claim Rejection- 35 U.S.C. § 112, second paragraph

Claims 1-19, 21, 23, 25, 32-35 and 37-41 are rejected as allegedly being indefinite for reciting the term "derived." (Office Action, page 6, paragraph 14) Applicants respectfully traverse the rejection. Applicants note that this term is explicitly discussed in the Specification on page 8, bottom paragraph. In addition, methods and publications regarding the Ig-derived binding domain are provided. One of skill in the art can read these passages and readily understand the current claims.

Also, in an effort to expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have amended claim 1 to include the limitation of claim 14, which should render the rejection moot. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

VI. Claim Rejection- 35 U.S.C. § 112, first paragraph

Claim 18 is rejected as allegedly failing to comply with the written description requirement. (Office Action, page 7, paragraph 15) Applicants disagree. However, in an effort to expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have deleted claim 18, which should render the rejection moot.

VII. Claim Rejection- 35 U.S.C. § 112, first paragraph

Claims 1-19, 21, 23, 25, 32-35 and 37-41 are rejected as allegedly being non-enabled. The Office admits that the invention is "enabling for an antibody construct comprising three heavy chain CDR regions and three light chain CDR regions." (Office Action, page 12, paragraph 17) However, the Office alleges that the specification "does not reasonably provide enablement for an antibody construct comprising fewer than all 6 CDR regions." (Office Action, page 12, paragraph 17) Applicants respectfully traverse the rejection.

To expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have amended claim 1 to include specific binding constructs describing CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3. As such, the invention is now brought into the enabled antibody embodiment as described by the Office. Therefore, Applicants respectfully request withdrawal of the rejection.

VIII. Claim Rejection- 35 U.S.C. § 112, first paragraph

Claims 37-40 are rejected as allegedly being non-enabled. The Office admits that the invention is "enabling for a method of inducing cytotoxicity in a cell expressing CD3." (Office Action, page 16, paragraph 18). However, the Office alleges that the specification "does not reasonably provide enablement for a method of preventing just any disease." (Office Action, page 16, paragraph 18). Applicants respectfully traverse the rejection.

In an effort to expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have amended claim 37 to remove the "preventing" term. Applicants believe the amendment should render the rejection moot. Therefore, Applicants respectfully request withdrawal of the rejection.

IX. Claim Rejection- 35 U.S.C. § 101

Claims 1-13, 15, 16, and 33 are rejected as allegedly being directed to non-statutory subject matter. Applicants respectfully traverse the rejection.

Applicants note that the invention is directed towards **deimmunized** cytotoxically active CD3 specific binding constructs. Deimmunized antibodies are not found in nature.

Additionally, deimmunized antibodies cannot be generated without the hand of man, and as such, cannot read on naturally occurring antibodies. Therefore, Applicants respectfully request withdrawal of the rejection.

X. Claim Rejection- 35 U.S.C. § 103- Bendig in view of Joliffe

Claims 1, 3, 5, 15-17, 32, 33-35 and 37-40 are rejected as allegedly being obvious over Bendig (WO 92/15683) in view of Joliffe (US 5,929,212). Specifically, the Office alleges that Bendig teaches molecules that comprise "a peptide that is identical to the instant SEQ ID No. 233" (Office Action, page 22, paragraph 24) However, the Office admits that Bendig "do[es] not teach an antibody that binds to CD3." (Office Action, page 22, paragraph 24) To remedy this deficiency, the Office uses Jolifee, which the Office states "teach[es] production [of] humanized recombinant antibody molecules that bind to CD3 and comprise a sequence that is identical to the instant SEQ ID Nos. 96, 88, 235, 156, and 157." (Office Action, page 22, paragraph 24) Applicants respectfully traverse the rejection.

A. Current Obviousness Standard

The Supreme Court recently reaffirmed the Graham factors for determining obviousness in KSR Int'l Co. v. Teleflex Inc. (No. 04-1350) (U.S., April 30, 2007). The Graham factors, as outlined by the Supreme Court in Graham et al. v. John Deere Co. of Kansas City et al., 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a), and held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed, and specifically stated:

> Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was ***an apparent reason to combine the known elements in the fashion claimed*** by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007) (emphasis added). As discussed below, the cited art cannot render the claimed invention obvious.

B. Bendig and/or Jolifee Do Not Teach Each and Every Element

When determining whether a claim is obvious, an examiner must make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (*citing In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

Applicants have amended claim 1 to recite to specific CDR-sequences that are not disclosed in either Bendig or Joliffe. Specifically, neither Bendig nor Joliffe disclose an Ig-derived second binding domain consisting of scFv, as correctly noted by the Examiner (lack of rejection of claim 14). Additionally, Applicants have amended claim 1 to include limitations of canceled claims 8, 10, 11 and 12. The Office has correctly noted that these claims are not obvious over either Bendig or Jolifee. Because Applicants have amended claim 1 to include the limitations found in claims 8, 10, 11, 12 and 14, Applicants believe the claims are clearly not obvious over Bendig or Jolifee.

C. Unexpected Results in the Claimed Invention

Even if Bendig and Jolifee taught every element of the claimed invention, there are unexpected results that one of ordinary skill in the art would not have been able to anticipate. When one considers the obviousness of a combination of known elements, the operative question is "whether the improvement [in combining elements found in the prior art] is more than the predictable use of [the] elements according to their established functions." MPEP § 2141(I),

citing *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007). "While obviousness does not require absolute predictability, *at least some degree of predictability is required.*" MPEP § 2143.02(II) (emphasis added). Evidence of unexpected results must be weighed against evidence supporting prima facie obviousness in making a final determination of the obviousness of the claimed invention. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA178) (See also MPEP 716.02(c))

Applicants disclose a CD3-specific binding construct that is deimmunized. However, deimmunized antibodies often loose their biological activity, i.e. exhibit a decreased binding affinity and/or cytotoxicity. Generation of deimmunized antibodies which retain their biological activity is not a trivial task. Very often, deimmunization does not result in a decreased immune response, or if it does, biological activity of the antibody is lost or decreased.

However, Applicants surprisingly found that CD3 specific binding constructs with a deimmunized domain comprising the CDR sequences as recited in claim 1 **have not lost their biological activity and even show a superior binding activity** and/or cytotoxicity when compared to prior art antibodies. Specifically it was found that CD3 specific binding constructs with variable heavy chain domains VH5 and VH7 (see specification page 76, table 9) which were deimmunized in accordance with the present invention exhibit improved binding affinity and/or cytotoxicity; see specification Examples 2, 4, 5, 8, and Figures 12, 13, and 15-18. Further, it was unexpectedly found that deimmunized cytotoxically active constructs show a characteristic sequence VKK in framework H1 and a ASGYTF transition sequence (See specification Example 7 and Figure 14).

In contrast, not all constructs with deimmunized variable heavy chain domains exhibit improved binding affinity and/or cytotoxicity (Specification, Example 2). For example, CD3 specific binding constructs with a deimmunized VH2 domain or VH3 domain even lost their binding affinity almost completely and showed only a similar binding as the negative control (Specification, Example 2).

Therefore, the CD3 specific binding construct with deimmunized VH5 and VH7 domains show a stronger binding affinity than the positive control (non-deimmunized anti-CD19 x anti-CD3 construct). Also an improved or at least comparable cytotoxicity of exemplary anti-CD3 x anti-CD19 and anti-CD3 x anti-EPCAM constructs of the present invention compared to positive controls are demonstrated. (Specification, Example 5 and Example 8.5 and Figures 13, 17 and 18). As such, none of the cited prior art documents prompts a person of skill in the art to arrive at the present invention.

XI. Claim Rejection- 35 U.S.C. § 103- Joliffe in view of Carr

Claims 1, 3, 5, 15-18, 32-35 and 37-40 are rejected as allegedly being obvious over Joliffe (US 5,929,212) in view of Carr (WO 2002/069232). The Office admits that Jolifee "do[es] not teach an antibody that comprises SEQ ID Nos. 233 or 234." (Office Action, page 25, paragraph 25) To remedy this deficiency, the Office uses Carr, which the Office states "teach[es] production of antibodies with reduced immunogenicity that bind to a number of antigens including GD2, Her2 and CD20." (Office Action, page 25, paragraph 25) Applicants respectfully traverse the rejection.

As noted in Section X(B), Applicants have amended claim 1 to recite to specific CDR-sequences that are not disclosed in either Joliffe or Carr. Specifically, neither Joliffe nor Carr disclose an Ig-derived second binding domain consisting of scFv, as correctly noted by the Examiner (lack of rejection of claim 14). Additionally, Applicants have amended claim 1 to include limitations of canceled claims 8, 10, 11 and 12. The Office has correctly noted that these claims are not obvious over either Jolifee or Carr. Because Applicants have amended claim 1 to include the limitations found in claims 8, 10, 11, 12 and 14, Applicants believe the claims are clearly not obvious over Jolifee or Carr.

Additionally, as noted in Section X(C), Applicants show unexpected results regarding the deimmunized CD3 specific binding constructs disclosed in the instant application. Specifically, Applicants show strong binding affinity than the positive control, which is contrary to most deimmunized antibodies which show a weaker or loss of biological activity after deimmunization.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

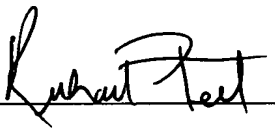
CONCLUSIONS

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition(s) for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date May 18, 2010

By 

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